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Several methods can be used for stereotactically guided injection of a neurotoxin to various intracranial targets, such as the pedunculopontine nuclei to decrease cholinergic neurotransmission, or the ventral tegmental area to decrease the release of dopamine to alleviate positive symptoms of a neuropsychiatric disorder. For example, a stereotactic magnetic resonance imaging (MRI) method relying on three-dimensional (3D) T1-weighted images for surgical planning and multiplanar T2-weighted images for direct visualization of the pedunculopontine nuclei or the ventral tegmental area, coupled with electrophysiological recording and injection guidance for unilateral or bilateral STN injection can be used. See e.g. Bejjani, B. P., et al., Bilateral Subthalamic Stimulation for Parkinson's Disease by Using Three-Dimensional Stereotactic Magnetic Resonance Imaging and Electrophysiological Guidance, J Neurosurg 92(4);615-25:2000.

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DOCUMENT-IDENTIFIER: US 20040180061 A1

TITLE: Botulinum toxin therapy for neuropsychiatric disorders

Pre-Grant Publication (PGPub) Document Number:
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Summary of Invention Paragraph:

[0007] Schizophrenia is a disorder that affects about one percent of the world population. Three general symptoms of schizophrenia are often referred to as positive symptoms, negative symptoms, and disorganized symptoms. Positive symptoms may include delusions (abnormal beliefs), hallucinations (abnormal perceptions), and disorganized thinking. Hallucinations may be auditory, visual, olfactory, or tactile.

Summary of Invention Paragraph:

[0008] Disorganized thinking may manifest itself in schizophrenic patients by disjointed speech and the inability to maintain logical thought processes. Negative symptoms may represent the absence of normal behavior. Negative symptoms include emotional flatness or lack of expression and may be characterized by social withdrawal, reduced energy, reduced motivation, and reduced activity. Catatonia may also be associated with negative symptoms of schizophrenia. The symptoms of schizophrenia should continuously persist for a duration of about six months in order for the patient to be diagnosed as schizophrenic. Based on the types of symptoms a patient reveals, schizophrenia may be categorized into subtypes including including catatonic schizophrenia, paranoid schizophrenia, and disorganized schizophrenia.

Summary of Invention Paragraph:

[0010] Although the cause of schizophrenia is not precisely known, there are several hypotheses regarding the causes. One hypothesis is that schizophrenia is associated with increased dopamine activity within the cortical and limbic areas of the brain. This hypothesis is supported by the therapeutic effects achieved by antipsychotic drugs that block certain dopamine receptors. In addition, amphetamine use may be associated with schizophrenia-like psychotic symptoms; amphetamines act on dopamine receptors.

Summary of Invention Paragraph:

[0011] Examples of antipsychotic drugs that may be used to treat schizophrenic patients include phenothizines, such as chlorpromazine and trifluopromazine; thioxanthenes, such as chlorprothixene; fluphenazine; butyrophenones, such as haloperidol; loxapine; mesoridazine; molindone; quetiapine; thiothixene; trifluoperazine; perphenazine; thioridazine; risperidone; dibenzodiazepines, such

as clozapine; and olanzapine. Although these agents may relieve the symptoms of schizophrenia, their administration may also result in undesirable side effects including Parkinson's disease-like symptoms (tremor, muscle rigidity, loss of facial facial expression); dystonia; restlessness; tardive dyskinesia; weight gain; skin problems; dry mouth; constipation; blurred vision; drowsiness; slurred speech; agranulocytosis.

Summary of Invention Paragraph:

[0013] Dopamine neurons may be organized into four major subsystems: the tuberoinfundibular system; the nigrostriatal system; the mesolimbic system; and the mesocortical system. The tuberoinfundibular dopaminergic system originates in cell bodies of the arcuate nucleus of the hypothalamus and projects to the pituitary stalk. This system may be involved in secondary neuroendocrine abnormalities in schizophrenia. The nigrostriatal dopaminergic system originates in the substantia nigra and projects primarily to the putamen and the caudate nucleus. The mesolimbic dopaminergic system originates in the ventral tegmental area and projects to the mesial component of the limbic system, which includes the nucleus accumbens, the nuclei of the stria terminalis, parts of the amygdala and hippocampus, the lateral septal nuclei, and the mesial frontal, anterior cingulate, and entorhinal cortex. The nucleus accumbens is a convergence site from the amygdala, hippocampus, entorhinal area, anterior cingulate area, and parts of the temporal lobe. Thus, the mesolimbic dopaminergic projection may modulate and transform information conveyed from the nucleus accumbens to the septum, hypothalamus, anterior cingulate area, and frontal lobes, and overactive modulation of the nucleus accumbens output to these areas may contribute to positive symptoms associated with schizophrenia. The mesocortical dopaminergic system originates in the ventral tegmental area and projects to the neocortex and heavily to the prefrontal cortex. This component may be important in the negative symptoms of schizophrenia.

Summary of Invention Paragraph:

[0016] Mania is a sustained form of euphoria that affects millions of people in the United States who suffer from depression. Manic episodes may be characterized by an elevated, expansive, or irritable mood lasting several days, and is often accompanied by other symptoms, such as, overactivity, overtalkativeness, social intrusiveness, increased energy, pressure of ideas, grandiosity, distractibility, decreased need for sleep, and recklessness. Manic patients may also experience delusions and hallucinations.

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[0018] Mania likely results from an imbalance in the chemical messengers within the brain. It has been proposed that mania may be attributed to a decline in acetylcholine. A decline in acetylcholine may result in a relatively greater level of norepinephrine. Administering phosphotidyl choline has been reported to alleviate the symptoms of mania.

Summary of Invention Paragraph:

[0020] Anxiety disorders may affect between approximately ten to thirty percent of the population, and may be characterized by frequent occurrence of symptoms of fear including arousal, restlessness, heightened responsiveness, sweating, racing heart, increased blood pressure, dry mouth, a desire to run or escape, and avoidance behavior. Generalized anxiety persists for several months, and is associated with motor tension (trembling, twitching, muscle aches, restlessness); autonomic hyperactivity (shortness of breath, palpitations, increased heart rate, sweating, cold hands), and vigilance and scanning (feeling on edge, exaggerated startle response, difficult in concentrating).

Summary of Invention Paragraph:

[0023] Alzheimer's disease is a degenerative brain disorder characterized by cognitive and noncognitive neuropsychiatric symptoms, which accounts for approximately 60% of all cases of dementia for patients over 65 years old.

Psychiatric symptoms are common in Alzheimer's disease, with psychosis (hallucinations and delusions) present in approximately fifty percent of affected patients. Similar to schizophrenia, positive psychotic symptoms are common in Alzheimer's disease. Delusions typically occur more frequently than hallucinations. Alzheimer's patients may also exhibit negative symptoms, such as disengagement, apathy, diminished emotional responsiveness, loss of volition, and decreased initiative.

Summary of Invention Paragraph:

[0025] It is possible that the psychotic symptoms of Alzheimer's disease may involve a shift in the concentration of dopamine or acetylcholine, which may augment a dopaminergic/cholinergic balance, thereby resulting in psychotic behavior. For example, it has been proposed that an increased dopamine release may be responsible for the positive symptoms of schizophrenia. This may result in a positive disruption of the dopaminergic/cholinergic balance. In Alzheimer's disease, the reduction in cholinergic neurons effectively reduces acetylcholine release resulting in a negative disruption of the dopaminergic/cholinergic balance. Indeed, antipsychotic agents that are used to relieve psychosis of schizophrenia are also useful in alleviating psychosis in Alzheimer's patients.

Summary of Invention Paragraph:

[0026] Several of the symptoms associated with the neuropsychiatric disorders appear appear to be, at least in part, attributed to hyperexcitability of neurons within the brain. This interpretation is supported by the pharmacology associated with current therapeutic treatments. For example, many of the antipsychotic treatments are directed to interfering with binding of dopamine to dopamine receptors, as discussed above. Similarly, mania and anxiety are often treated with benzodiazepines, which enhance the inhibitory effects of GABA-mediated inhibition. U.S. Pat. No. 6,306,403 discloses intracranial administration of a botulinum toxin to treat various movement disorders. Additionally, it is known that stereotactic procedures can be used to administer a pharmaceutical to a discrete brain area to successfully alleviate a parkinsonian tremor. See e.g. Pahapill P.A., et al., Tremor arrest with thalamic microinjections of muscimol in patients with essential tremor, Ann Neur 46(2); 249-252 (1999).

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[0029] The genus Clostridium has more than one hundred and twenty seven species, grouped according to their morphology and functions. The anaerobic, gram positive bacterium Clostridium botulinum produces a potent polypeptide neurotoxin, botulinum toxin, which causes a neuromuscular illness in humans and animals referred to as botulism. The spores of Clostridium botulinum are found in soil and can grow in improperly sterilized and sealed food containers of home based canneries, which are the cause of many of the cases of botulism. The effects of botulism typically appear 18 to 36 hours after eating the foodstuffs infected with a Clostridium botulinum culture or spores. The botulinum toxin can apparently pass unattenuated through the lining of the gut and attack peripheral motor neurons. Symptoms of botulinum toxin intoxication can progress from difficulty walking, swallowing, and speaking to paralysis of the respiratory muscles and death.

Summary of Invention Paragraph:

[0077] Methods for treating neuropsychiatric disorders comprise the step of intracranially administering a neurotoxin to a patient. The neurotoxin is administered in a therapeutically effective amount to alleviate at least one symptom of the disorder. The neurotoxin alleviates the symptoms associated with the disorder by reducing secretions of neurotransmitter from the neurons exposed to the neurotoxin.

Summary of Invention Paragraph:

[0080] The neurotoxin is administered to a site within the brain that is believed to be involved in the disorder being treated. The neurotoxin may be administered to

a lower brain region, the pontine region, the pedunculopontine nucleus, the locus ceruleus, or the ventral tegmental area, for example. The neurotoxin may alleviate the symptom that is associated with hyperactive neurotransmitter release. The neurotoxin may also restore a balance between two neuronal systems to alleviate the disorder. The neurotoxin administered to the patient may inhibit acetylcholine release from cholinergic neurons, may inhibit dopamine release from dopaminergic neurons, may inhibit the release of norepinephrine from noradrenergic neurons.

Summary of Invention Paragraph:

[0081] The neuropsychiatric disorders treated in accordance with the methods disclosed herein include, and are not limited to, schizophrenia, Alzheimer's disease, mania, and anxiety. The neurotoxin can alleviate a positive symptom associated with the neuropsychiatric disorder, for example schizophrenia, and can alleviate the symptoms within a few hours after administration.

Detail Description Paragraph:

[0097] Local intracranial administration of a botulinum toxin, according to the present invention, by injection or implant to a nucleus of the brain having neurons believed to be involved in symptoms associated with neuropsychiatric disorder provides a superior alternative to systemic administration of pharmaceuticals to patients to alleviate the symptoms associated with neuropsychiatric disorders.

Detail Description Paragraph:

[0103] A neurotoxin, such as a botulinum toxin, can be intracranially administered according to the present disclosed methods in amounts of between about 10.sup.-4 U/kg to about 1 U/kg. A dose of about 10.sup.-4 U/kg can result in a suppressant effect if delivered to a small nuclei. Intracranial administration of less than about 10.sup.-4 U/kg does not result in a significant or lasting therapeutic result. An intracranial dose of more than 1 U/kg of a neurotoxin, such as a botulinum toxin, can pose a significant risk of denervating other afferent or efferent neuronal systems adjacent to such nuclei. However, it is also believed that the neurons within these nuclei are not as sensitive to the neurotoxin as are neurons at the neuromuscular junction. Accordingly, administration of a neurotoxin, such as botulinum toxin, to an intracranial target tissue involved in neuropsychiatric disorders effectively reduces symptoms associated with the disorders without causing significant cognitive dysfunction. Thus, the methods of the present invention provide more selective treatment with fewer undesirable side effects than current systemic therapeutic regimes.

Detail Description Paragraph:

[0104] A preferred range for intracranial administration of a botulinum toxin, such as botulinum toxin type A, so as to achieve an tremor suppressant effect in the patient treated is from about 10.sup.-4 U/kg to about 1 U/kg. Less than about 104.sup.2 U/kg can result in a relatively minor, though still observable, neuropsychiatric symptom suppressant effect. A more preferred range for intracranial intracranial administration of a botulinum toxin, such as botulinum toxin type A, so as to achieve the desired effect in the patient treated is from about 10.sup.-3 U/kg to about 1 U/kg. Less than about 10.sup.-3 U/kg can result in the desired therapeutic effect being of less than the optimal or longest possible duration. A most preferred range for intracranial administration of a botulinum toxin, such as botulinum toxin type A, so as to achieve a desired tremor suppressant effect in the patient treated is from about 0.1 units to about 20 units. Intracranial administration of a botulinum toxin, such as botulinum toxin type A, in this preferred range can provide dramatic therapeutic success.

Detail Description Paragraph:

[0106] As set forth above, I have discovered that administration of a neurotoxin to a patient suffering from a neuropsychiatric disorder surprisingly provides effective and long lasting treatment of the neuropsychiatric disorder, and reduces the symptoms associated with the disorder. In its most preferred embodiment, the

present invention is practiced by intracranial injection or implantation of botulinum toxin type A.

Detail Description Paragraph:

[0113] Several methods can be used for stereotactically guided injection of a neurotoxin to various intracranial targets, such as the pedunculopontine nuclei to decrease cholinergic neurotransmission, or the ventral tegmental area to decrease the release of dopamine to alleviate positive symptoms of a neuropsychiatric disorder. For example, a stereotactic magnetic resonance imaging (MRI) method relying on three-dimensional (3D) T1-weighted images for surgical planning and multiplanar T2-weighted images for direct visualization of the pedunculopontine nuclei or the ventral tegmental area, coupled with electrophysiological recording and injection guidance for unilateral or bilateral STN injection can be used. See e.g. Bejjani, B. P., et al., Bilateral Subthalamic Stimulation for Parkinson's Disease by Using Three-Dimensional Stereotactic Magnetic Resonance Imaging and Electrophysiological Guidance, J Neurosurg 92(4);615-25:2000.

Detail Description Paragraph:

[0116] A 48 year old male presents with reduced motivation and interest in daily life. The patient indicates that he hears voices. The patient is monitored regularly for six months. The symptoms gradually worsen throughout the monitoring period, and the patient is diagnosed with schizophrenia. Using CAT scan or MRI assisted stereotaxis, as set forth in Example 1 above, 2 units of a botulinum toxin type A (such as BOTOX.RTM. or about 8 units of Dysport.RTM.) is injected into the pedunculopontine nucleus. The patient is discharged within 48 hours and with a few (1-7) days enjoys significant improvement of the positive symptoms of schizophrenia. The positive symptoms of schizophrenia remain significantly alleviated for between about 2 to about 6 months. For extended therapeutic relief, one or more polymeric implants incorporating a suitable quantity of a botulinum toxin type A can be placed at the target tissue site.

Detail Description Paragraph:

[0118] A 68 year female previously diagnosed and treated for schizophrenia wishes to try a new therapeutic treatment. She seeks the advice of a physician who recommends botulinum toxin therapy. Using CAT scan or MRI assisted stereotaxis, as set forth in Example 1 above, from 10 to about 50 units of a botulinum toxin type B preparation (such as Neurobloc.RTM. or Innervate.TM.) is injected into the pedunculopontine nuclei. The patient is discharged within 48 hours and with a few (1-7) days enjoys significant improvement of the positive symptoms. Her hallucinations almost completely disappear. The positive symptoms remain significantly alleviated for between about 2 to about 6 months. For extended therapeutic relief, one or more polymeric implants incorporating a suitable quantity of a botulinum toxin type B can be placed at the target tissue site.

Detail Description Paragraph:

[0125] Although the patient's loss of memory does not recover fully, the psychotic symptoms the patient was exhibiting are reduced and remain substantially alleviated for between about 2 months to about 6 months per toxin injection or for between about 1 to 5 years depending upon the particular release characteristics of the implant polymer and the quantity of neurotoxin loaded therein.

Detail Description Paragraph:

[0127] The patient of example 5 above can be equivalently treated using the same protocol and approach to target the locus ceruleus with between about 1 unit and about 1000 units of a botulinum toxin type B, C.sub.1, D, E, F or G in aqueous solution or in the form of a suitable neurotoxin implant. With such a treatment, the psychotic symptoms subside within 1-7 days, and remain substantially alleviated for between about 2-6 months per toxin injection or for between about 1 to 5 years depending upon the particular release characteristics of the implant polymer and the quantity of neurotoxin loaded therein.

Detail Description Paragraph:

[0130] The patient's manic symptoms can subside within 1-7 days, and can remain substantially alleviated for between about 2 months to about 6 months per toxin injection or for between about 1 to 5 years depending upon the particular release characteristics of the implant polymer and the quantity of neurotoxin loaded therein. Notably, there can be significant attenuation of hallucinations. In addition, the patient has a substantially more controlled behavioral pattern.

Detail Description Paragraph:

[0132] The patient of example 7 above can be equivalently treated using the same protocol and approach to target with between about 1 unit and about 1000 units of a botulinum toxin type B, C.sub.1, D, E, F or G in aqueous solution or in the form of a suitable neurotoxin implant. With such a treatment, the symptoms can subside within 1-7 days, and can remain substantially alleviated for between about 2-6 months per toxin injection or for between about 1 to 5 years depending upon the particular release characteristics of the implant polymer and the quantity of neurotoxin loaded therein.

Detail Description Paragraph:

[0139] 1. the symptoms, such as the symptoms associated with hyperactive neuronal systems of a neuropsychiatric disorder can be dramatically reduced.

Detail Description Paragraph:

[0140] 2. the symptoms of a neuropsychiatric disorder can be reduced for from about two to about four months per injection of neurotoxin and for from about one year to about five years upon use of a controlled release neurotoxin implant.

CLAIMS:

1. A method for alleviating a symptom of a neuropsychiatric disorder, the method comprising a step of administering to a patient with a symptom of a neuropsychiatric disorder a therapeutically effective amount of a Clostridial neurotoxin, wherein the Clostridial neurotoxin is administered to an intracranial site which is associated with the symptom of the neuropsychiatric disorder, thereby alleviating the symptom of the neuropsychiatric disorder.

7. The method of claim 1, wherein the symptom alleviating effect persists for between about 1 month and about 5 years.

12. The method of claim 1, wherein the administration of the neurotoxin alleviates a symptom of the neuropsychiatric disorder that is associated with hyperactive neurotransmitter release from neurons.

13. The method of claim 1, wherein administering the Clostridial neurotoxin restores a balance between at least two neuronal systems that release different neurotransmitters, thereby alleviating the symptom of the neuropsychiatric disorder.

14. The method of claim 1, wherein administering the Clostridial neurotoxin decreases an acetylcholine release from a cholinergic neuron, thereby alleviating the symptom of the neuropsychiatric disorder.

15. The method of claim 1, wherein administering the Clostridial neurotoxin decreases a dopamine release from a dopaminergic neuron, thereby alleviating the symptom of the neuropsychiatric disorder.

16. The method of claim 1, wherein administering of the Clostridial neurotoxin decreases a norepinephrine release from a noradrenergic neuron, thereby alleviating the symptom of the neuropsychiatric disorder.

17. A method for treating a symptom of a neuropsychiatric disorder, the method comprising a step of administering to a patient with a symptom of a neuropsychiatric disorder a therapeutically effective amount of a botulinum toxin, wherein the botulinum toxin is administered to an intracranial site which is associated with the symptom of the neuropsychiatric disorder, thereby treating the symptom of the neuropsychiatric disorder.

20. A method for treating a neuropsychiatric disorder, the method comprising a step of administering to a patient with a symptom of a neuropsychiatric disorder a therapeutically effective amount of a botulinum toxin, wherein the botulinum toxin is administered to an intracranial site which is associated with the symptom of the neuropsychiatric disorder, thereby treating the symptom of the neuropsychiatric disorder by reducing neurotransmitter release from neurons contributing to the symptom of the neuropsychiatric disorder within about four months after the administration of the botulinum toxin.

21. A method for treating schizophrenia, the method comprising a step of administering to a patient with schizophrenia a therapeutically effective amount of a botulinum toxin, wherein the botulinum toxin is administered to an intracranial site which is associated with a symptom of schizophrenia, thereby treating schizophrenia.

23. A method for alleviating a symptom of a neuropsychiatric disorder, the method comprising the step of administering to a peripheral site of a patient with a symptom of a neuropsychiatric disorder a therapeutically effective amount of a Clostridial neurotoxin.

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[0097] Local intracranial administration of a botulinum toxin, according to the present invention, by injection or implant to a nucleus of the brain having neurons believed to be involved in symptoms associated with neuropsychiatric disorder provides a superior alternative to systemic administration of pharmaceuticals to patients to alleviate the symptoms associated with neuropsychiatric disorders.

Detail Description Paragraph:

[0103] A neurotoxin, such as a botulinum toxin, can be intracranially administered according to the present disclosed methods in amounts of between about 10.sup.-4 U/kg to about 1 U/kg. A dose of about 10.sup.-4 U/kg can result in a suppressant effect if delivered to a small nuclei. Intracranial administration of less than about 10.sup.-4 U/kg does not result in a significant or lasting therapeutic result. An intracranial dose of more than 1 U/kg of a neurotoxin, such as a botulinum toxin, can pose a significant risk of denervating other afferent or efferent neuronal systems adjacent to such nuclei. However, it is also believed that the neurons within these nuclei are not as sensitive to the neurotoxin as are neurons at the neuromuscular junction. Accordingly, administration of a neurotoxin, such as botulinum toxin, to an intracranial target tissue involved in neuropsychiatric disorders effectively reduces symptoms associated with the disorders without causing significant cognitive dysfunction. Thus, the methods of the present invention provide more selective treatment with fewer undesirable side effects than current systemic therapeutic regimes.

Detail Description Paragraph:

[0104] A preferred range for intracranial administration of a botulinum toxin, such as botulinum toxin type A, so as to achieve an tremor suppressant effect in the patient treated is from about 10.sup.-4 U/kg to about 1 U/kg. Less than about 104.sup.2 U/kg can result in a relatively minor, though still observable, neuropsychiatric symptom suppressant effect. A more preferred range for intracranial intracranial administration of a botulinum toxin, such as botulinum toxin type A, so as to achieve the desired effect in the patient treated is from about 10.sup.-3 U/kg to about 1 U/kg. Less than about 10.sup.-3 U/kg can result in the desired therapeutic effect being of less than the optimal or longest possible duration. A most preferred range for intracranial administration of a botulinum toxin, such as botulinum toxin type A, so as to achieve a desired tremor suppressant effect in the patient treated is from about 0.1 units to about 20 units. Intracranial administration of a botulinum toxin, such as botulinum toxin type A, in this preferred range can provide dramatic therapeutic success.

Detail Description Paragraph:

[0106] As set forth above, I have discovered that administration of a neurotoxin to a patient suffering from a neuropsychiatric disorder surprisingly provides effective and long lasting treatment of the neuropsychiatric disorder, and reduces the symptoms associated with the disorder. In its most preferred embodiment, the

present invention is practiced by intracranial injection or implantation of botulinum toxin type A.

Detail Description Paragraph:

[0113] Several methods can be used for stereotactically guided injection of a neurotoxin to various intracranial targets, such as the pedunclopontine nuclei to decrease cholinergic neurotransmission, or the ventral tegmental area to decrease the release of dopamine to alleviate positive symptoms of a neuropsychiatric disorder. For example, a stereotactic magnetic resonance imaging (MRI) method relying on three-dimensional (3D) T1-weighted images for surgical planning and multiplanar T2-weighted images for direct visualization of the pedunclopontine nuclei or the ventral tegmental area, coupled with electrophysiological recording and injection guidance for unilateral or bilateral STN injection can be used. See e.g. Bejjani, B. P., et al., Bilateral Subthalamic Stimulation for Parkinson's Disease by Using Three-Dimensional Stereotactic Magnetic Resonance Imaging and Electrophysiological Guidance, J Neurosurg 92(4);615-25:2000.

Detail Description Paragraph:

[0116] A 48 year old male presents with reduced motivation and interest in daily life. The patient indicates that he hears voices. The patient is monitored regularly for six months. The symptoms gradually worsen throughout the monitoring period, and the patient is diagnosed with schizophrenia. Using CAT scan or MRI assisted stereotaxis, as set forth in Example 1 above, 2 units of a botulinum toxin type A (such as BOTOX.RTM. or about 8 units of Dysport.RTM.) is injected into the pedunclopontine nucleus. The patient is discharged within 48 hours and with a few (1-7) days enjoys significant improvement of the positive symptoms of schizophrenia. The positive symptoms of schizophrenia remain significantly alleviated for between about 2 to about 6 months. For extended therapeutic relief, one or more polymeric implants incorporating a suitable quantity of a botulinum toxin type A can be placed at the target tissue site.

Detail Description Paragraph:

[0118] A 68 year female previously diagnosed and treated for schizophrenia wishes to try a new therapeutic treatment. She seeks the advice of a physician who recommends botulinum toxin therapy. Using CAT scan or MRI assisted stereotaxis, as set forth in Example 1 above, from 10 to about 50 units of a botulinum toxin type B preparation (such as Neurobloc.RTM. or Innervate.TM.) is injected into the pedunclopontine nuclei. The patient is discharged within 48 hours and with a few (1-7) days enjoys significant improvement of the positive symptoms. Her hallucinations almost completely disappear. The positive symptoms remain significantly alleviated for between about 2 to about 6 months. For extended therapeutic relief, one or more polymeric implants incorporating a suitable quantity of a botulinum toxin type B can be placed at the target tissue site.

Detail Description Paragraph:

[0125] Although the patient's loss of memory does not recover fully, the psychotic symptoms the patient was exhibiting are reduced and remain substantially alleviated for between about 2 months to about 6 months per toxin injection or for between about 1 to 5 years depending upon the particular release characteristics of the implant polymer and the quantity of neurotoxin loaded therein.

Detail Description Paragraph:

[0127] The patient of example 5 above can be equivalently treated using the same protocol and approach to target the locus ceruleus with between about 1 unit and about 1000 units of a botulinum toxin type B, C.sub.1, D, E, F or G in aqueous solution or in the form of a suitable neurotoxin implant. With such a treatment, the psychotic symptoms subside within 1-7 days, and remain substantially alleviated for between about 2-6 months per toxin injection or for between about 1 to 5 years depending upon the particular release characteristics of the implant polymer and the quantity of neurotoxin loaded therein.

Detail Description Paragraph:

[0130] The patient's manic symptoms can subside within 1-7 days, and can remain substantially alleviated for between about 2 months to about 6 months per toxin injection or for between about 1 to 5 years depending upon the particular release characteristics of the implant polymer and the quantity of neurotoxin loaded therein. Notably, there can be significant attenuation of hallucinations. In addition, the patient has a substantially more controlled behavioral pattern.

Detail Description Paragraph:

[0132] The patient of example 7 above can be equivalently treated using the same protocol and approach to target with between about 1 unit and about 1000 units of a botulinum toxin type B, C.sub.1, D, E, F or G in aqueous solution or in the form of a suitable neurotoxin implant. With such a treatment, the symptoms can subside within 1-7 days, and can remain substantially alleviated for between about 2-6 months per toxin injection or for between about 1 to 5 years depending upon the particular release characteristics of the implant polymer and the quantity of neurotoxin loaded therein.

Detail Description Paragraph:

[0139] 1. the symptoms, such as the symptoms associated with hyperactive neuronal systems of a neuropsychiatric disorder can be dramatically reduced.

Detail Description Paragraph:

[0140] 2. the symptoms of a neuropsychiatric disorder can be reduced for from about two to about four months per injection of neurotoxin and for from about one year to about five years upon use of a controlled release neurotoxin implant.

CLAIMS:

1. A method for alleviating a symptom of a neuropsychiatric disorder, the method comprising a step of administering to a patient with a symptom of a neuropsychiatric disorder a therapeutically effective amount of a Clostridial neurotoxin, wherein the Clostridial neurotoxin is administered to an intracranial site which is associated with the symptom of the neuropsychiatric disorder, thereby alleviating the symptom of the neuropsychiatric disorder.
7. The method of claim 1, wherein the symptom alleviating effect persists for between about 1 month and about 5 years.
12. The method of claim 1, wherein the administration of the neurotoxin alleviates a symptom of the neuropsychiatric disorder that is associated with hyperactive neurotransmitter release from neurons.
13. The method of claim 1, wherein administering the Clostridial neurotoxin restores a balance between at least two neuronal systems that release different neurotransmitters, thereby alleviating the symptom of the neuropsychiatric disorder.
14. The method of claim 1, wherein administering the Clostridial neurotoxin decreases an acetylcholine release from a cholinergic neuron, thereby alleviating the symptom of the neuropsychiatric disorder.
15. The method of claim 1, wherein administering the Clostridial neurotoxin decreases a dopamine release from a dopaminergic neuron, thereby alleviating the symptom of the neuropsychiatric disorder.
16. The method of claim 1, wherein administering of the Clostridial neurotoxin decreases a norepinephrine release from a noradrenergic neuron, thereby alleviating the symptom of the neuropsychiatric disorder.

17. A method for treating a symptom of a neuropsychiatric disorder, the method comprising a step of administering to a patient with a symptom of a neuropsychiatric disorder a therapeutically effective amount of a botulinum toxin, wherein the botulinum toxin is administered to an intracranial site which is associated with the symptom of the neuropsychiatric disorder, thereby treating the symptom of the neuropsychiatric disorder.

20. A method for treating a neuropsychiatric disorder, the method comprising a step of administering to a patient with a symptom of a neuropsychiatric disorder a therapeutically effective amount of a botulinum toxin, wherein the botulinum toxin is administered to an intracranial site which is associated with the symptom of the neuropsychiatric disorder, thereby treating the symptom of the neuropsychiatric disorder by reducing neurotransmitter release from neurons contributing to the symptom of the neuropsychiatric disorder within about four months after the administration of the botulinum toxin.

21. A method for treating schizophrenia, the method comprising a step of administering to a patient with schizophrenia a therapeutically effective amount of a botulinum toxin, wherein the botulinum toxin is administered to an intracranial site which is associated with a symptom of schizophrenia, thereby treating schizophrenia.

23. A method for alleviating a symptom of a neuropsychiatric disorder, the method comprising the step of administering to a peripheral site of a patient with a symptom of a neuropsychiatric disorder a therapeutically effective amount of a Clostridial neurotoxin.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw D.
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